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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,047	02/17/2004	Steven P. Gygi	57559 (70207)	8390
21874 7590 09/16/2008 EDWARDS ANGELL PALMER & DODGE LLP P.O. BOX 55874 BOSTON, MA 02205				
EXAMINER				
SIEN, BIN				
ART UNIT		PAPER NUMBER		
1657				
MAIL DATE		DELIVERY MODE		
09/16/2008		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

**Application No.**

10/781,047

**Applicant(s)**

GYGI ET AL.

**Examiner**

BIN SHEN

**Art Unit**

1657

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 June 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 6-22 and 25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 6-22, 25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-884)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

DETAILED ACTION

*Status of the Claims*

Claims 6-22 and 25 are presented for examination.

*Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 6-22 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desiderio (J Chromatography B 1999;731:3-21) in view of Gerber et al. (Anal. Chem. 2001, 73:1651-1657).

Desiderio teaches a method for determining the presence/quantity of a target polypeptide in a mixture of different polypeptides by providing a mixture of human tissue extracts (from human with metabolic defects and normal control-page 5, 2.1 and 2.2), adding two known quantity of labeled (labeled differently with stable isotopes) peptide internal standard (page 5, 2.4), treating the mixture with a protease (trypsin-page 7, 2.6), fragmenting the peptides in the mixture by multistage mass spectrometry (tandem mass spectrometer-page 7, 2.8), determining the ratio of labeled fragments to unlabeled fragments and calculating the quantity of the target polypeptide in the mixture (page 7, 2.10.1 and page 8, 2.10.2). Peptides are separated by HPLC chromatograph (page 6, under Chromatograph, 2.5.1-2.5.4) and the fractions (eluent and co-eluent) are shown in Fig. 5-7. The presence/quantity of target polypeptide is diagnostic of a cell state where the cell state is representative of an abnormal physiological response (human pituitary macroadenomas-page 9, 3.1), and the target polypeptide is determined in at least two mixtures (abstract and for details see pages 9-14, pages 14-17).

Desiderio does not teach a single peptide internal standard in the method.

Gerber teaches a chromatography/mass spectrometry method for determining multiple enzyme activities in human cell lysates using a single internal standard (page 1652, right column, 2<sup>nd</sup> full paragraph). Gerber also teaches that the internal standard is chemically identical to the enzyme product and contain isotope (page 1652, right column, 2<sup>nd</sup> full paragraph, lines 4-7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Desiderio by using a single peptide internal standard in the method because protease activity is used and Gerber teaches the use of a single internal standard which is identical to the enzyme product (peptide as the product of protease) in the same chromatography/mass spectrometry method. One would have been motivated to make the modification because Desiderio et al. specifically described a method for determining the presence/quantity of a target polypeptide in a mixture of different polypeptides with two peptide internal standard, and would reasonably have expected success because Gerber teach the use of an internal standard that is chemically identical to the enzyme product in the same method (page 1652, right column, 2<sup>nd</sup> full paragraph). One internal standard is recognized as equivalent of two internal standard for the same purpose (see MPEP §2144.06), thus using one internal standard that is chemically identical to the enzyme product as taught by Gerber for the predictable result of determining the presence/quantity of a target peptide is obvious.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments file 6/3/2008 have been fully considered but they are not persuasive.

Applicant argues that neither the Desiderio or Gerber references teach or suggest the use of proteolysis of the labeled peptide internal standard and any target peptide; neither the Desiderio or Gerber references teach or suggest the measurement of target peptides and modified target peptides.

It is the examiner's position that Desiderio teaches the use of proteolysis of the labeled peptide internal standard (trypsinolysis of peptide standards- $\beta$ -endorphin, see page 7, left column, under 2.6.) and any target peptide (tryptic peptide, see page 6, right column, 3rd paragraph under 2.5.3.); and that Desiderio teaches the measurement of target peptides (the quantification of a neuropeptide, see page 7, right column, under 2.10.1.). This is a situation of order of mixing. In the instant claims, the larger peptide is cleaved with the spiked mass altered peptide fragment internal reference already present. In Desiderio, the mass altered peptide fragment is added to the proteolytically fragmented protein so that both the mass altered and the corresponding non-mass-unaltered peptides will be in the same mixture that is subsequently analyzed. This is a functionally equivalent process and is deemed *prima facie* obvious.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

### *Conclusion*

No claim is allowed.

Certain papers related to this application may be submitted to Art Unit 1657 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Bin Shen, Ph.D., whose telephone number is (571) 272-9040. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to her office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571) 272-0925.

*B Shen*

Art Unit 1657

/JON P WEBER/

Supervisory Patent Examiner, Art Unit 1657